Defunctioning Stoma Reduces Symptomatic Anastomotic Leakage After Low Anterior Resection of the Rectum for Cancer

A Randomized Multicenter Trial

Peter Matthiessen, MD, PhD, Olof Hallböök, MD, PhD,‡ Jörgen Rutegård, MD, PhD,* Göran Simert, MD, PhD,† and Rune Sjödahl, MD, PhD‡*

Objective: The aim of this randomized multicenter trial was to assess the rate of symptomatic anastomotic leakage in patients operated on with low anterior resection for rectal cancer and who were intraoperatively randomized to a defunctioning stoma or not.

Summary Background Data: The introduction of total mesorectal excision surgery as the surgical technique of choice for carcinoma in the lower and mid rectum has led to decreased local recurrence and improved oncological results. Despite these advances, perioperative morbidity remains a major issue, and the most feared complication is symptomatic anastomotic leakage. The role of the defunctioning stoma in regard to anastomotic leakage is controversial and has not been assessed in any randomized trial of sufficient size.

Methods: From December 1999 to June 2005, a total of 234 patients were randomized to a defunctioning loop stoma or no loop stoma. Loop ileostomy or loop transverse colostomy was at the choice of the surgeon. Inclusion criteria for randomization were expected survival >6 months, informed consent, anastomosis ≤7 cm above the anal verge, negative air leakage test, intact anastomotic rings, and absence of major intraoperative adverse events.

Results: The overall rate of symptomatic leakage was 19.2% (45 of 234). Patients randomized to a defunctioning stoma (n = 116) had leakage in 10.3% (12 of 116) and those without stoma (n = 118) in 28.0% (33 of 118) (odds ratio = 3.4; 95% confidence interval, 1.6–6.9; $P < 0.001$). The need for urgent abdominal reoperation was 8.6% (10 of 116) in those randomized to stoma and 25.4% (30 of 118) in those without ($P < 0.001$). After a follow-up of median 42 months (range, 6–72 months), 13.8% (16 of 116) of the initially defunctioned patients still had a stoma of any kind, compared with 16.9% (20 of 118) those not defunctioned (not significant). The 30-day mortality after anterior resection was 0.4% (1 of 234) and after elective reversal a defunctioning stoma 0.9% (1 of 111). Median age was 68 years (range, 32–86 years), 45.3% (106 of 234) were females, 79.1% (185 of 234) had preoperative radiotherapy, the level of anastomosis was median 5 cm, and intraoperative blood loss 550 mL, without differences between the groups.

Conclusion: Defunctioning loop stoma decreased the rate of symptomatic anastomotic leakage and is therefore recommended in low anterior resection for rectal cancer.

(*Ann Surg* 2007;246: 207–214)

From the *Department of Surgery, at *Örebro University Hospital, Örebro, Sweden; †Department of Surgery, Höglandssjukhuset, Eksjö, Sweden; and ‡Department of Surgery, Linköping University Hospital, Linköping, Sweden, for the RECTODES study group (Rectal Cancer Trial on Defunctioning Stoma).

The following units participated in the RECTODES study group (REctal Cancer Trial On DEfunctioning Stoma) and the surgeons responsible for the trial were:

Lars Påhlman, Akademiska Sjukhuset, Uppsala
Peter Andersson, Blekingesjukhuset, Karlskrona
Johan Ottosson, Centralsjukhuset, Kristianstad
Björn Öjerskog, Sahlgrenska Universitetssjukhuset/Östra, Göteborg
Torbjörn Holm, Karolinska Universitetssjukhuset/Solna, Stockholm
Asbjörn Österberg, Mora Lasarett
Inger Magnusson, Södersjukhuset, Stockholm
Ingvar Syk, Universitetssjukhuset MAS, Malmö
George Falco de Mats, Karlskoga Lasarett
Michael Dahlberg, Sunderby Sjukhus, Luleå
Disa Kalman, Vrinnevisjukhuset, Norrköping
Bo Fagerkvist, Sjukhuset i Lidköping
Ulf Kressner, Uddevalla Sjukhus
Martin Jansson, Karolinska Universitetssjukhuset/Huddinge, Stockholm
Conny Svensson, Östersunds Lasarett
Åke Öberg, Norrlands Universitetssjukhus, Umeå
Rolf Hellberg, Mälarsjukhuset, Eskilstuna
Håkan Olsson, Skellefteå Lasarett
Göran Simert, Höglandssjukhuset, Eksjö
Olof Hallböök, Universitetssjukhuset, Linköping
Peter Matthiessen, Universitetssjukhuset, Örebro

Supported by a grant from the Research Committee, Örebro County Council, Sweden.

Reprints: Peter Matthiessen, MD, PhD, Department of Surgery, Örebro University Hospital, 701 85 Örebro, Sweden. E-mail: peter.matthiessen@orebroll.se.

ISSN: 0003-4932/07/24602-0207
DOI: 10.1097/SLA.0b013e3180603024

The understanding of the mesorectal spread in rectal cancer and the introduction of total mesorectal excision surgery as the surgical technique of choice for carcinoma in the lower and mid rectum has led to decreased local recurrence and improved oncologic outcome.[1–3] Improved results have also been demonstrated by centralization of surgery and educational programs for colorectal surgeons.[4,5] Despite these

important advances, postoperative morbidity and early mortality after anterior resection of the rectum remain important issues.[6] The overall early postoperative mortality rate is reported to be between 1% and 8%.[4] Symptomatic anastomotic leakage is the most feared complication and has been reported to occur in between 1% and 24%,[7–12] and when present, the associated risk of postoperative mortality is increased to between 6% and 22%.[11] One can anticipate that anastomotic leakage occurs in a medically fragile patient, or after a technically difficult operation, or if intraoperative adverse events were present. However, anastomotic leakage also occurs in patients with no obvious risk factors.[13] The difficulty in predicting anastomotic leakage, including patients considered to be at low risk, has generated several studies in recent years with the aim of identifying risk factors.[10–12,14] The most common risk factors for leakage in retrospective studies with multivariable analysis are low anastomosis and male gender.[11,12] One risk factor demonstrated in retrospective studies with multivariable analysis is the absence of a defunctioning stoma.[9,15] However, data are conflicting and in population-based retrospective studies, including multivariable analysis, lower leakage rates have not been demonstrated in patients with defunctioning stoma.[16] There are 3 randomized studies addressing this issue, by Graffner et al,[17] Pakkastie et al,[8] and Pimentel et al,[18] comprising 50, 38 and 36 randomized patients, respectively. In these studies, no firm conclusions could be drawn due to small numbers.

The primary aim of the present trial was to assess whether there was a difference in the rate of symptomatic anastomotic leakage in patients randomized intraoperatively to fecal deviation or not. When the present trial was planned in the late 1990s, there was no consensus in Sweden regarding type of defunctioning stoma; therefore, the study protocol accepted the use of loop ileostomy as well as loop transverse colostomy. Secondary aims were the assessment of postoperative morbidity and the outcome regarding reversal of the defunctioning stoma.

METHODS AND PATIENTS

Study Design

All hospitals in Sweden performing rectal cancer surgery in 1999 (n = 65) were asked to participate in the present study, the REctal Cancer Trial On DEfunctioning Stoma (RECTODES). All patients operated on with anterior resection of the rectum for cancer during the period of participation of each hospital were analyzed. To assess possible selection bias, the randomized patients were compared with the nonrandomized patients. Data on the randomized patients were obtained from the RECTODES study protocol. Data on patients not randomized were obtained from the Swedish Rectal Cancer Registry.[19] All randomized patients were assessed according to the study protocol: preoperatively, during the hospital stay, at one and at 12 months after the initial rectal resection, and, in patients with a defunctioning stoma, at the time of the reversal of the stoma, and when the patient had been free of stoma for 12 months. The study was approved by the local ethics committee of the Linköping healthcare region and by the local ethic committees of each of the participating hospitals.

Inclusion Criteria and Randomization Procedure

Preoperative inclusion criteria were biopsy proven adenocarcinoma of the rectum located at ≤15 cm above the anal verge measured with a rigid rectoscope, age ≥18 years, informed consent, ability to understand the study information, and estimated survival of >6 months as judged by the surgeon. Intraoperative inclusion criteria were anastomosis at ≤7 cm above the anal verge, negative air leakage test, intact anastomotic stapler rings, and the absence of major intraoperative adverse events as judged by the operating surgeon.

If no exclusion criteria were present, the patient was randomized intraoperatively after the construction and testing of the anastomosis, by opening a sealed envelope in the operating room. All patients had preoperative bowel preparation and prophylactic antibiotics according to the standard treatment of each hospital. Furthermore, preoperative irradiation, chemotherapy, and the use of pelvic drainage were at the choice of the surgeon.

Definition of Anastomotic Leakage

The definition of anastomotic leakage was clinical; peritonitis caused by leakage from any staple line, rectovaginal fistula, and pelvic abscess without radiologically proven leakage mechanism were included. Leakage was verified by clinical (digital palpation, inspection of drain contents), endoscopic (rigid rectoscopy, flexible sigmoidoscopy), or radiologic (rectal contrast study, CT scan) investigations. Radiologically demonstrated leakage without clinical symptoms was not included.

Study Hypothesis and Statistical Analysis

The study hypothesis was that a defunctioning stoma decreases the rate of symptomatic leakage from 15% to 7.5%. With a statistical power of 80% and a level of significance at 5%, randomization of 220 patients was required. For comparison between groups, the χ^2 test was used for categorical data and the Mann-Whitney U test for continuous data.

A P value of less than 5% was considered significant. For statistical analysis, the SPSS for Windows version 12 (Chicago, IL) and the Statistix version 8 (Tallahassee, FL) were used.

RESULTS

Comparison Between Randomized and Nonrandomized Patients

Between December 1999 and June 2005, a total of 234 patients were randomized by 21 hospitals participating for a mean of 21 months during this time period. Of all the anterior resections performed by the participating hospitals, 28.5% (234 of 821) were randomized and 71.5% (587 of 821) were not. The most frequent reasons for not randomizing patients were the presence of intraoperative adverse events prompting a defunctioning stoma (28%), absence of patient consent (25%), anastomosis >7 cm above the anal verge (18%), and

TABLE 1. Reasons for Not Randomizing Patients Operated on for Anterior Resection of the Rectum for Cancer in 21 Swedish Hospitals During the Time of Participation of Each Hospital

Reason	%
Preop. reason	
No patient consent	25
Patient not asked by the surgeon	6
Patient unable to understand trial information	2
Advanced stage IV cancer or T4 cancer	10
Major comorbidity	3
Two primary cancers	2
Rectal cancer recurrence	1
Planned as partial mesorectal excision	1
Other reasons	1
Intraop. reason	
Intraop. adverse events	28
Whereof technically difficult operation	14
Pos. air leakage test	5
Anastomotic stapler rings not intact	4
Major intraop. bleeding	4
Perforation of the tumor or rectum	1
Anastomosis >7 cm	18
Anastomosis considered ultra-low	3

Based on prospectively reported nonrandomized patients (n = 307); retrospectively reported nonrandomized patients or data missing (n = 280).

advanced TNM stage IV cancer or T4 cancer (10%) (Table 1). The randomized patients had a lower proportion of TNM stage IV cancer and more often had preoperative radiotherapy compared with those not randomized, but in all other respects there were no differences between the groups (Table 2).

Patient Demography and Operative Details in the Randomized Patients

The operation time was longer in those randomized to a stoma, 220 versus 200 minutes; otherwise, there were no differences between the groups regarding patient demography and intraoperative details (Table 3).

Anastomotic Leakage

The total rate of symptomatic anastomotic leakage was 19.2% (45 of 234 patients). Randomization yielded 116 patients with defunctioning stoma and 118 without defunctioning stoma. In patients with a defunctioning stoma, a symptomatic leakage occurred in 10.3% (12 of 116), compared with 28.0% (33 of 118) of those without defunctioning stoma (28.0% vs. 10.3%; odds ratio [OR] = 3.4; 95% confidence interval [CI], 1.6–6.9; $P < 0.001$) (Table 4). In 27 patients (60% of those with a leak), the symptomatic leakage was diagnosed during the initial hospital stay at median day 8 (range, 3–18 days). The other 18 patients (40% of those with a leak) with symptomatic leakage were initially discharged from hospital on median day 10 (range, 7–31 days) and had their leakage diagnosed upon readmission during a second hospital stay on median day 24 (range, 13–172 days). Nine of 106 women (8.5%) developed rectovaginal fistula, which accounted for 9 of 45 of all the leakages and 9 of 21 of all leakages in women. In the patients initially not defunctioned who had a rectovaginal fistula, 6 of 7 were reoperated with a laparotomy and a loop stoma on median day 26 (range, 12–152 days). In those initially not defunctioned who had a leakage other than rectovaginal fistula, 22 of 26 patients were reoperated with a laparotomy and loop stoma. There was no difference in leakage rates between those irradiated and not irradiated (20.7% vs. 13.3%; not significant). The most common ways of initial diagnosis of the leakage were by CT scan (n = 13), rectal contrast study (n = 11), and rectal digital palpation (n = 8).

Anastomotic Leakage and Type of Anastomosis

All 234 anastomoses were made with a circular stapler device, and none was hand-sewn. A J-pouch was constructed in 43.6% (102 of 234), a side-to-end anastomosis in 38.9% (91 of 234), an end-to-end anastomosis in 16.2% (n = 38 of 234), and 1.3% (3 of 234) the type of anastomosis was not

TABLE 2. Study Population Demography

	Not Randomized* (n = 587)	Randomized to Stoma (n = 116)	Randomized to No Stoma (n = 118)	*P*†
Age (yr) [median (range)]	69 (28–90)	68 (32–86)	67.5 (4–84)	NS‡
Female gender	44.3%	39.7% (46/116)	50.8% (60/118)	NS§
Body mass index	Not stated	25.0 (19.3–35.9)	24.8 (21.1–36.6)	—‡
ASA score 1 or 2	Not stated	83.2%	89.2%	—§
Tumor level above the anal Verge (cm) [median (range)]	10 (3–15)	10 (4–15)	10 (3–15)	NS‡
TNM stage IV cancer	17.0%	4.3%	3.4%	<0.001§
Preop. radiotherapy	54.9%	81.0% (94/116)	77.1% (91/118)	<0.001§

The total cohort of patients operated on with low anterior resection for rectal cancer in the population served by the participating hospitals during their time period of participation in this trial.

*Data on patients not randomized from the Swedish Rectal Cancer Registry (SRCR). Data from the SRCR available until December 31, 2004. Data from January 1 to June 30, 2005 not included in the analysis.

†Comparison between the nonrandomized patients and the group of all randomized patients.

‡Mann-Whitney *U* test.

§χ^2 test.

NS indicates not significant; ASA, American Society of Anesthesiologists.

TABLE 3. Operative Details in the Randomized Patients

	Stoma* (n = 116)	No Stoma† (n = 118)
Operation time (min)	220 (110–605)	200 (100–541)
Intraop. bleeding (mL)	550 (50–4500)	550 (50–2500)
Anastomotic level (cm) [median (range)]	5 (2–7)	5 (2–7)
Defunctioning stoma (%)	99.1	0.8

Patients operated on with low anterior resection for rectal cancer in the 21 hospitals participating in the present study from December 1999 to June 2005 and randomized to defunctioning stoma (n = 116) or no defunctioning stoma (n = 118).

*Including 1 case of violation of the study protocol analyzed on intention to treat basis.

†Including 1 case of violation of the study protocol analyzed on intention to treat basis.

stated. There were no differences in leakage rates between the different types of anastomoses: J-pouch 21.6% (22 of 102), side to end 19.8.% (18 of 91), and end to end 13.2% (5 of 38) (not significant, χ^2 test for trend).

Duration of Hospital Stay

The initial hospital stay was median 11 days (range, 5–81 days) for the whole group. For patients initially defunctioned, it was median 13 days (range, 6–60 days); and for patients initially not defunctioned, it was median 9 days (range, 5–81 days). When adding the time for scheduled and unscheduled readmission, hospital stay was median 18 days (range, 8–66 days) and 10 days (range, 5–85 days) in initially defunctioned and nondefunctioned patients, respectively (Table 5).

Outcome in Patients Initially Defunctioned

Stoma Reversal

In the 116 patients with a defunctioning stoma, 112 (96.6%) had a loop ileostomy and 4 a transverse loop colostomy. Of these patients, 86.2% (100 of 116) had their stoma reversed at median 5 months (range, 1–22 months) after the rectal excision, while 16 had not been reversed for various reasons at median 42 months of follow-up (range, 6–72 months) (Table 6). Of 12 patients with defunctioning stoma and leakage, 8 were electively reversed after median 8 months (range, 2–22 months) of whom one later had a permanent end sigmoidostomy because of poor anorectal function after reversal of the defunctioning stoma. Subsequently, 7 of 12 patients with leakage in this group were free of stoma at median 42 months (range, 6–72 months) follow-up.

Reoperations

Seven patients (6.0%) were urgently reoperated during the initial hospital stay on median day 10 (range, 7–37 days), one patient was urgently reoperated after hospital discharge after 2 months, 2 patients were urgently reoperated after stoma reversal, and 2 were electively reoperated after stoma reversal. One patient with an abscess after stoma reversal was percutaneously drained (Table 7).

Outcome in Patients Initially Not Defunctioned

Reoperation for Leakage and Stoma Reversal

In 118 patients without defunctioning stoma, 33 patients (28.0%) developed symptomatic leakage, of which 28 were reoperated urgently with laparotomy and loop ileostomy (n = 25) or permanent end sigmoidostomy (n = 3). Five patients were treated with anorectal drainage but without abdominal surgery ("conservative treatment"). Eleven of 25 patients with a loop stoma (44.0%) had their stomas reversed after median 10 months (range, 4–11 months) and 3 of these patients later had a permanent end sigmoidostomy fashioned because of poor anorectal function. Thus, 8 of 25 patients with leakage were free of stoma at median 42 months (range, 6–72 months) follow-up. One patient died in septic complications after 8 months and 5 reoperations, and one patient died in septic complications after an elective conversion of a loop ileostomy to a permanent sigmoidostomy, 30 months after the rectal resection

Other Reoperations

Two patients, not defunctioned, were urgently reoperated during the initial hospital stay (postoperative day 18 and 21), and 2 patients were electively reoperated (after 7 and 22 months) (Table 7). One urgently defunctioned patient developed an enterocutaneous fistula from the loop ileostomy, and this fistula was managed conservatively.

TABLE 4. Symptomatic Anastomotic Leakage Rate

	Stoma (n = 116)	No Stoma (n = 118)	*P*
Leakage, all patients	10.3% (12/116)	28.2% (33/118)	<0.001*
Leakage, men	10.0% (7/70)	29.3% (17/58)	0.005*
Leakage, women	10.9% (5/46)	26.7% (16/60)	0.043*
Leakage, women, not including rectovaginal fistula	6.5% (3/46)	15.0% (9/60)	0.172*
Leakage, all patients, not including rectovaginal fistula	8.6% (10/116)	22.2% (26/118)	0.003*
Patients with stoma (loop stoma or end colostomy) at median 42 mo (range, 6–72 mo) follow-up	13.8% (16/116)	16.9% (20/118)	NS*

Aspects on symptomatic leakage rate and prevailing stoma in patients operated on with low anterior resection for rectal cancer and randomized to defunctioning stoma (n = 116) or no defunctioning stoma (n = 118).

*χ^2 test.

NS indicates not significant.

TABLE 5. Hospital Stay

	Stoma (n)	No Stoma (n)	*P*
Initial hospital stay (days)	n = 116	n = 118	
Median (range)	13 (6–60)	9 (5–81)	<0.001*
Hospital stay including scheduled and unscheduled readmission† (days)	n = 116	n = 118	
Median (range)	18 (8–66)	10 (5–85)	<0.001*
Initial hospital stay, no leakage, (days)	n = 104	n = 85	
Median (range)	11.5 (6–60)	9 (5–21)	<0.001*
Hospital stay, no leakage, scheduled and unscheduled readmission† (days)	n = 104	n = 85	
Median (range)	17 (8–66)	9 (5–21)	<0.001*
Hospital stay, leakage, scheduled and unscheduled readmission† (days)	n = 12	n = 33	
Median (range)	31 (12–42)	27 (8–85)	NS*

Aspects on hospital stay in patients operated on with low anterior resection for rectal cancer and randomized to defunctioning stoma (n = 116) or no defunctioning stoma (n = 118).
*Mann-Whitney *U* test.
†Including reversal of defunctioning stoma.
NS indicates not significant.

TABLE 6. Reoperations

	Stoma (n = 116)	No Stoma (n = 118)	*P*
Urgent reoperation, any type, any hospital stay	10 (8.6%)	30 (25.4%)	<0.001*
Elective reoperation, any type, any hospital stay	2 (1.7%)	2 (1.7%)	
Urgent reoperation, initial hospital stay			
Laparotomy and defunctioning loop stoma	—	25	
Laparotomy and end sigmoid stoma	—	3	
Laparotomy and drainage	1	—	
Small bowel perforation	—	1	
Small bowel obstruction, no relation to stoma	3†	—	
Small bowel obstruction because of stomal hernia	2‡	—	
Enterocutaneous fistula from loop ileostomy	1§	—	
Wound dehiscence	1‖	1	
Urgent reoperation after stoma reversal			
Anastomotic leakage in ileoileal anastomosis	1	—	
Peritonitis due to perforation of the colon	1¶	—	
Elective reoperation with stoma present			
Stomal hernia	—	1	
Elective reoperation after stoma reversal			
Chronic wound in stoma cicatrix	1	—	
Colovesical fistula, permanent colostomy	1	—	
Chronic small bowel obstruction	—	1	

Reoperations in patients operated on with low anterior resection of the rectum for cancer randomized to defunctioning stoma (n = 116) or no defunctioning stoma (n = 118).
*χ^2 test.
†Including one operation upon urgent readmission.
‡Including urgent reversal of the stoma in one patient.
§Including urgent reversal of the stoma.
‖One patient operated 3 times.
¶Patient died of septic complications on postoperative day 18.

Early Mortality

The 30-day mortality after anterior resection was 0.4% (1 of 234). An 82-year-old man with hypertension and epilepsy, residing alone, randomized to defunctioning stoma, discharged on day 8, was readmitted on day 13 without fever and with normal CRP because of a minor infection in the stoma wound. He was treated with antibiotics and discharged on day 21. The pathology report demonstrated a TNM stage

TABLE 7. Reasons for Prevailing Stoma

	Defunctioned Initially (n = 16)	Not Defunctioned Initially (n = 20)
Poor anorectal function	4	4
Anastomotic stricture	—	3
Conversion to end colostomy at urgent reoperation	—	3
Poor medical condition	2	1
Patient refusal of further surgery	1	1*
Loop ileostomy at 24 mo, deemed permanent	—	1
No decision of reversal at median 13 mo (range, 6–22 mo)	—	4
Progressive liver metastases	5	1
New non colorectal cancer	1	1
Waiting for scheduled reversal	2	1
Unexpected death before reversal	1	—

Reasons for prevailing stoma (loop stoma or end colostomy) in patients operated on with low anterior resection of the rectum for cancer initially defunctioned (n = 16) or initially not defunctioned (n = 20) at follow-up of median 42 mo (range, 6–72 mo).

*Anastomotic leakage after reversal of loop ileostomy and reoperated with a second loop ileostomy.

I cancer. He was found dead in his home on postoperative day 29. Autopsy revealed no signs of anastomotic leakage or intra-abdominal infection, and the final cause of death was deemed cardiac arrhythmia.

The 30-day mortality after elective reversal of a defunctioning stoma was 0.9% (1 of 111). An 84-year-old man with pulmonary disease randomized to defunctioning stoma and without leakage after the anterior resection had the defunctioning stoma reversed 7 months after the anterior resection and was discharged after an uneventful postoperative course on day 5. He was readmitted and urgently reoperated on postoperative day 10 due to peritonitis and a perforation of the colon was found. Postoperatively pneumonia, myocardial infarction, and multiorgan failure developed and death occurred on postoperative day 18.

Violation of the Study Protocol

In 3 patients (1.3%), there was violation of the study protocol. One patient was randomized to no stoma before the integrity of the anastomotic rings was verified and because of defective anastomotic rings the patient had a defunctioning stoma. One patient was converted from low anterior resection to a low Hartmann's procedure after randomization because of massive presacral bleeding, which needed packing. Two days later, the patient was reoperated with construction of a low anastomosis and a defunctioning stoma.

In 1 patient randomized to defunctioning stoma, previously operated with open cholecystectomy and a jejunoileal shunt because of obesity and, loop ileostomy as well as loop transverse colostomy were abandoned by the surgeon because of a short distal ileum and massive post cholecystectomy adhesions. These patients were analyzed on an intention to treat basis and none developed symptomatic leakage.

DISCUSSION

In this randomized multicenter trial, patients without defunctioning stoma leaked in 28.0% compared with 10.3% in those defunctioned. (OR = 3.4; 95% CI, 1.6–6.9; $P < 0.001$), a result not previously demonstrated in any randomized trial. The overall rate of symptomatic leakage of 19.2% in this trial is higher than in several previously presented investigations,[7,11] comparable with some series[21] and lower than some.[11] The leakage rate may appear high taking into account that the operations were considered free of adverse events at the end of the procedure when randomization was performed. However, it is of importance that the definition of symptomatic anastomotic leakage in the present study included leakage from any staple line, as well as rectovaginal fistula, pelvic abscess without radiologically proven leakage mechanism, and also leakages diagnosed after hospital discharge.

Defunctioning stoma in low anterior resection has been considered to decrease the leakage rate by some, including one large retrospective multicenter study by Peeters et al, in which defunctioned patients leaked in 9%, compared with 24% of those not defunctioned.[15] Others have argued that the stoma mitigates the consequences of a leakage but does not lower the leakage rate itself, as was the result in a large retrospective multicenter study by Gastinger et al, in which the leakage rate was 14% with and without defunctioning stoma.[16] However, the weakness of these studies, as well as any nonrandomized study, is that it was the surgeon who decided which patient should have a defunctioning stoma or not, and that possible selection bias cannot be ruled out in retrospect. The present study, which is based on a power calculation with a sufficient number of patients, has demonstrated a lower leakage rate in patients randomized to a defunctioning stoma. Therefore, we conclude that the presence of a defunctioning stoma significantly decreases the rate of symptomatic leakage.

The need for urgent laparotomy for any reason was increased in patients randomized to no stoma compared with those defunctioned, 25% and 9%, respectively. In the patients randomized to no stoma, 28 of 30 with urgent laparotomy were operated on because of leakage and had a stoma. This was not the situation in those initially defunctioned in whom urgent abdominal surgery was performed only in one patient because of symptomatic leakage, but in 9 of 10 for reasons related to the loop stoma or small bowel obstruction. Thus, not only were the patients not defunctioned operated urgently more often, but the reasons to operate were also different. There was a tendency that leakage in patients not defunctioned was associated with poorer anorectal function compared with those with leakage initially defunctioned. This observation is based on the finding that, albeit limited numbers, nearly two thirds of those initially defunctioned (7 of 12) who developed leakage could have their stoma permanently reversed, compared with only one third (8 of 25) of those initially not defunctioned.

Of the initially defunctioned patients, 13.8% had a stoma of any kind after a follow-up of median 3.5 years, compared with 16.9% in those initially not defunctioned (not significant). This puts focus on the idea of the defunctioning

stoma, sometimes called temporary stoma, which in one of 6 patients, regardless of initial defunctioning or not, in reality became a permanent stoma. The expression temporary stoma is therefore not appropriate.

The 30-day mortality rate after elective reversal of electively and urgently defunctioned patients was 0.9% (1 of 111), which compares to 0.5% recently described.[16,20] This additional risk of mortality should be included in the total early mortality.

Twenty percent of the leakages (9 of 45) were rectovaginal fistulas. The reported incidence of rectovaginal fistulas following rectal excision is often low,[21] but findings comparable to the present study were recently reported by Kosugi et al.[22] In the present trial, 6 of 7 patients with rectovaginal fistulas, initially not defunctioned, were reoperated with a laparotomy and a defunctioning stoma. This compares with the nondefunctioned patients with symptomatic leakage other than rectovaginal fistula of whom 22 of 26 were reoperated with a laparotomy and a stoma. This finding supports both the view that rectovaginal fistula should be regarded as any other symptomatic anastomotic leakage, and the definition of anastomotic leakage chosen in this trial.

Hospital stay was longer in patients randomized to defunctioning stoma, median 13 versus 9 days. This difference in length of initial hospital stay can probably be explained by the time needed for the patient to learn how to handle the stoma appliance. If adding scheduled and unscheduled readmissions, the difference was even more pronounced, median 18 compared with 10 days, and obviously affects healthcare costs. Late leakages, diagnosed after hospital discharge, are not often reported in the literature.[23]

In the present study, 40% (18 of 45) of the symptomatic leakages were diagnosed after hospital discharge, upon readmission on median day 24. Late leakages may have a tendency to be underdiagnosed, or even underreported, as indicated in one meta-analysis.[24]

In the present study, the randomized patients had preoperative radiotherapy more often than the nonrandomized patients (79.1% vs. 54.9%), which could be one factor explaining the high leak rate as preoperative radiotherapy has been shown to be an independent risk factor in retrospective multivariate analysis.[12,14] Moreover, there were fewer patients with TNM stage IV cancer (3.9% vs. 17.0%). The increased proportion of stage IV cancer in the nonrandomized group explains to a certain degree the decreased proportion of irradiated patients.

Moreover, these findings could possibly also represent a selection bias in the way that the randomized patients, classified as ASA score 1 or 2 in 86%, were considered as more fit and that there were fewer contraindications for preoperative radiotherapy, although this cannot be proved since ASA score is not registered in the Swedish Rectal Cancer Registry.[19]

The issue of whether to use a defunctioning loop ileostomy or loop colostomy has been the subject of much debate.[25,26] The participating surgeons in this trial clearly demonstrated a preference for the loop ileostomy, which was used in 97% (112 of 116) of all the elective defunctioning stomas and in all (25 of 25) of the urgent defunctioning stomas. The use of pelvic drainage in rectal cancer surgery has recently been questioned.[27,28] In the present trial, the use of pelvic drainage was at the choice of the surgeon, which resulted in pelvic drainage in 97% (227 of 234) of the patients.

The proportion of eligible patients randomized is not often stated in surgical trials and needs consideration also in this trial, in which less than a third of the patients (28.5%) were randomized. Importantly, however, the most frequent exclusion criteria were the presence of intraoperative adverse events and patient refusal to participate, which accounted for more than half of the reported excluded patients; and because of the nature of these exclusion criteria, they could not be influenced by the surgeon. All of these factors must be considered when evaluating to what degree the results of this trial can be generalized and applied on other patient populations.

CONCLUSION

This randomized multicenter trial has demonstrated a decreased rate of symptomatic anastomotic leakage in defunctioned patients in low anterior resection, a result not previously shown in any randomized trial. Based on these results, and taking into account all aspects of the defunctioning stoma, we can recommend the use of a defunctioning stoma in low anterior resection of the rectum.

ACKNOWLEDGMENTS

The authors thank Anders Magnusson, Department of Medical Statistics, Örebro University Hospital, for statistical advice, and Robert Johansson, Oncological Centre, University Hospital, Umeå, for providing data from the Swedish Rectal Cancer Registry.

REFERENCES

1. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery: the clue to pelvic recurrence? *Br J Surg*. 1982;69:613–616.
2. Quirke P, Durdey P, Dixon MF, et al. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection: histopathological study of lateral tumour spread and surgical excision. *Lancet*. 1986;2: 996–999.
3. Wibe A, Eriksen MT, Syse A, et al. Total mesorectal excision for rectal cancer: what can be achieved by a national audit? *Colorectal Dis*. 2003;5:471–477.
4. Smedh K, Olsson L, Johansson H, et al. Reduction of postoperative morbidity and mortality in patients with rectal cancer following the introduction of a colorectal unit. *Br J Surg*. 2001;88:273–277.
5. Martling A, Holm T, Rutqvist LE, et al. Impact of a surgical training programme on rectal cancer outcomes in Stockholm. *Br J Surg*. 2005; 92:225–229.
6. Bokey EL, Chapuis PH, Hughes WJ, et al. Morbidity, mortality and survival following resection for carcinoma of the rectum at Concord Hospital. *Aust NZ J Surg*. 1990;60:253–259.
7. Enker WE, Merchant N, Cohen AM, et al. Safety and efficacy of low anterior resection for rectal cancer: 681 consecutive cases from a specialty service. *Ann Surg*. 1999;230:544–552; discussion 552–554.
8. Pakkastie TE, Ovaska JT, Pekkala ES, et al. A randomized study of colostomies in low colorectal anastomoses. *Eur J Surg*. 1997;163:929–933.
9. Dehni N, Schlegel RD, Cunningham C, et al. Influence of a defunctioning stoma on leakage rates after low colorectal anastomosis and colonic J pouch-anal anastomosis [see comment]. *Br J Surg*. 1998;85:1114–1117.

10. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. *Ann Surg*. 2004;240: 260–268.
11. Rullier E, Laurent C, Garrelon JL, et al. Risk factors for anastomotic leakage after resection of rectal cancer [see comment]. *Br J Surg*. 1998;85:355–358.
12. Matthiessen P, Hallbook O, Andersson M, et al. Risk factors for anastomotic leakage after anterior resection of the rectum. *Colorectal Dis*. 2004;6:462–469.
13. Poon RT, Chu KW, Ho JW, et al. Prospective evaluation of selective defunctioning stoma for low anterior resection with total mesorectal excision. *World J Surg*. 1999;23:463–467; discussion 467–468.
14. Eriksen MT, Wibe A, Norstein J, et al. Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. *Colorectal Dis*. 2005;7:51–57.
15. Peeters KC, Tollenaar RA, Marijnen CA, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. *Br J Surg*. 2005;92:211–216.
16. Gastinger I, Marusch F, Steinert R, et al. Protective defunctioning stoma in low anterior resection for rectal carcinoma. *Br J Surg*. 2005;92:1137–1142.
17. Graffner H, Fredlund P, Olsson SA, et al. Protective colostomy in low anterior resection of the rectum using the EEA stapling instrument: a randomized study. *Dis Colon Rectum*. 1983;26:87–90.
18. Pimentel JM, Duarte A, Patricio J. The role of a protecting stoma in low anterior resection with TME and colonic J-pouch for rectal cancer; results of a prospective randomized trial [Abstract]. *Colorectal Dis* 2003;5(suppl 2):P83.
19. Pahlman L, Bohe M, Cedermark B, et al. The Swedish Rectal Cancer Registry. *Br J Surg*. In press.
20. Hallbook O, Matthiessen P, Leinskold T, et al. Safety of the temporary loop ileostomy. *Colorectal Dis*. 2002;4:361–364.
21. Fleshner PR, Schoetz DJ Jr, Roberts PL, et al. Anastomotic-vaginal fistula after colorectal surgery. *Dis Colon Rectum*. 1992;35:938–943.
22. Kosugi C, Saito N, Kimata Y, et al. Rectovaginal fistulas after rectal cancer surgery: incidence and operative repair by gluteal-fold flap repair. *Surgery*. 2005;137:329–336.
23. DuBrow RA, David CL, Curley SA. Anastomotic leaks after low anterior resection for rectal carcinoma: evaluation with CT and barium enema. *AJR Am J Roentgenol*. 1995;165:567–571.
24. Bruce J, Krukowski ZH, Al-Khairy G, et al. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. *Br J Surg*. 2001;88:1157–1168.
25. Rullier E, Le Toux N, Laurent C, et al. Loop ileostomy versus loop colostomy for defunctioning low anastomoses during rectal cancer surgery. *World J Surg*. 2001;25:274–277; discussion 277–278.
26. Law WL, Chu KW, Choi HK. Randomized clinical trial comparing loop ileostomy and loop transverse colostomy for faecal diversion following total mesorectal excision. *Br J Surg*. 2002;89:704–708.
27. Urbach DR, Kennedy ED, Cohen MM. Colon and rectal anastomoses do not require routine drainage: a systematic review and meta-analysis. *Ann Surg*. 1999;229:174–180.
28. Petrowsky H, Demartines N, Rousson V, et al. Evidence-based value of prophylactic drainage in gastrointestinal surgery: a systematic review and meta-analyses. *Ann Surg*. 2004;240:1074–1084; discussion 1084–1075.